Amendments to the Drawings

The attached sheet of drawings includes changes to Figure 1A. This sheet, which includes Figure 1A, replaces the original sheet including Figure 1A. In Figure 1A, the total number of nucleotides has been corrected to recite "2311."

REMARKS

Amendments to the Specification

Applicants have amended paragraphs [0023], [0024] and [0143] by deleting the hyperlinks recited therein. Applicants have further amended paragraphs [0023], [0024] and [0028] to recite SEQ ID NO: identifiers as required.

Applicants have amended paragraph [0153] to delete reference to Figure 6, on account of its apparent omission from the instant specification.

The amendments constitute no new matter; Applicants respectfully request their entry.

The Amendments to the Claims

Applicants have canceled cancel claims 1-2 and 7-8 and 11 herein.

Applicants have amended claim 4 to (a) rewrite it in independent form and correct its dependency from canceled claim 1; (b) delete "substantially" and paragraph (ii), and (c) recite high stringency conditions in new paragraph (ii). Support for the amendment is found on page 19, paragraph [0044].

Applicants have amended claim 12 to properly depend from claim 4.

Applicants have added claims 43 and 44. Support for the amendment is found *e.g.,* in paragraph [0043] of the specification.

In sum, upon entry of this amendment, claims 4, 5, 12, and 43-44 will be pending. None of the above amendments constitutes new matter; their entry is respectfully requested.

The Amendments to the Drawings

Figure 1A, which previously recited that the total number of nucleotides was "2308" has been corrected to recite "2311." The amendment is supported by Figure 1A as filed.

THE OFFICE ACTION

The Objections to the IDS and the International Search Report

The Office Action has stated that references cited in the International Search Report for International Patent Application PCT/AU02/000542, and Applicants' Information Disclosure Statement filed on October 4, 2004 were considered and acknowledged, respectively, but will not be listed on any patent resulting from this application because the references listed therein were not in a format in compliance with 37 C.F.R. § 1.98(a)(1). In response, Applicants submit herewith a PTO-1449 form, with the references listed therein, in compliance with 37 C.F.R. § 1.98(a)(1). Accordingly, Applicants respectfully request that the Examiner initial the PTO-1449 form after consideration of the references listed therein, and return to Applicants a copy of the form initial by the Examiner.

The Objection to the Disclosure

The Office Action has objected to the embedded hyperlinks in paragraphs [0024] and [0143] of the instant specification. Applicants note that an embedded hyperlink also appears in paragraph [0023]. In response, Applicants have amended paragraphs [0023], [0024] and [0143] to delete reference to the hyperlinks. Accordingly, Applicants respectfully submit that the objection is rendered moot.

The Office Action has objected to the "SUMMARY OF SEQUENCE IDENTIFIERS" on page 12-14 as being unclear in disclosing the structural differences between SEQ ID NO:6 and SEQ ID NO:20. The Office Action further notes that the title of "Example 11" contains a typographical error.

Applicants respectfully submit that, as the Office Action indicated, there is no difference in SEQ ID NO:6 and SEQ ID NO:20. Applicants had inadvertently assigned SEQ ID NOs: to the sequences disclosed in the alignment shown in Figure 1C (*i.e.*, SEQ ID NO:20 and 21) independently of the sequences disclosed in the Sequence Listing (SEQ ID NO:4 and 6). Applicants submit that the above explanation clarifies the Examiner's question regarding the sequences disclosed in SEQ ID NO:6 and 20.

With respect to the Office Action's allegation that Example 11 contains a typographical error ("f" recited instead of "of"), Applicants have reviewed the specification as filed and have not identified any mistake in the title of Example 11. Applicants, however, stand ready to correct any typographical error the Examiner identifies.

The Office Action has further objected to the specification under 37 C.F.R. §1.821(d) as failing to provide a sequence identifier for each individual sequence. As discussed above, Applicants have amended the descriptions of Figures 1A, 1C, 2A and 2B to recite the required SEQ ID NOs. Applicants have also, as discussed *infra*, amended the sequence listing to include a sequence identifier for the nucleic acid sequence disclosed in Figure 1A.

The Substitute Sequence Listing

Applicants provide herewith in paper (30 pages) and computer readable form (two disks) a substitute sequence listing that includes a sequence identifier (SEQ ID NO:41) for the nucleic acid sequence disclosed in Figure 1A. Applicants note that Figure 1A erroneously recited that the total nucleotide length of the nucleic acid sequence shown is 2308. The correct length of the nucleotide sequence is 2311. The correction is noted on the replacement sheet of Figure 1A (discussed *supra*) and in the substitute Sequence Listing submitted herewith. Applicants further note that the SEQ ID NOs: 22-40 were amended to reflect the actual genus species where available. Source organisms were identified by the GenBank accession numbers cited in connection with the SEQ ID NOs. This amendment is made to better characterize the sequence and is fully supported by the specification as filed. The amendment constitutes no new matter. Applicants respectfully request the entry of the substitute Sequence Listing.

Applicants also submit herewith a Statement to Support Filing and Submission In Accordance with 37 C.F.R. §§ 1.821-1.825.

The Structural Relationship Between SEQ ID NO:5 and SEQ ID NO:6

The Office Action contends that there is no common structural relationship between the nucleotide of SEQ ID NO:5 and the polypeptide of SEQ ID NO:6. The Office

Action states that SEQ ID NO:5 is missing a codon corresponding to the Asp amino acid of SEQ ID NO:6 at position 211.

Applicants appreciate the Examiner's careful review of the sequence listing. Applicants have reviewed the sequence listing as filed in the instant application and the priority documents. Applicants acknowledge that there is a codon missing from SEQ ID NO:5 which would code for Asp211 of SEQ ID NO:6. In view thereof, Applicants have amended claims 1 and 2 to recite that the polypeptide or a derivative or homolog thereof which *in situ* forms part of the extracellular matrix (ECM) in an animal, comprises a von Willebrand Factor A (VA)-related domain encoded by a nucleotide sequence having at least 95% or 99% similarity to SEQ ID NO:5, which could encode a polypeptide of SEQ ID NO:6. Applicants reserve the right to address the apparent omission of codon in SEQ ID NO:5 at a future time in a manner consistent with United States Patent and Trademark Office procedures.

The Certified Priority Document

The Office Action has acknowledged Applicants' claim for foreign priority under 35 U.S.C. §119(a)-(d), but states that no certified copies of the priority document has been received from the International Bureau. The Examiner requests a courtesy copy. Applicants submit herewith at Exhibit 1 a photocopy of the certified priority document and further submit that a certified copy of the priority document will be provided at the time patentable subject matter is found.

The Objections to the Claims

The Office Action has objected to claims 7 and 11 for reciting "a set forth" instead of "as set forth." Applicants have canceled claims 7 and 11, rendering the objections moot.

THE REJECTIONS

The Rejections Under 35 U.S.C. § 112, Second Paragraph

The Claims Are Clear And Definite

The Office Action has rejected claims 1, 4, 7 and 11-12 under 35 U.S.C. § 112, 2nd paragraph, allegedly because the term "substantially" in claims 1, 4, 7 and 11 is indefinite. The Examiner further alleges that claims 11 and 12 are indefinite because they fail to further limit the polypeptide of claim 1 (from which claims 11-12 depend). The Office Action has also rejected claims 11-12 as failing to further limit the polypeptide as recited in claim 1.

Applicants have canceled claims 1, 7 and 11, rendering the rejections thereof moot. Applicants have amended claim 4. As amended, Applicants submit that the claims are now are now clear and definite. Accordingly, Applicants respectfully request that the rejections to pending claims 4 and 12 be withdrawn.

The Rejections Under 35 U.S.C. § 101

The Claims Are Drawn To Statutory Subject Matter

The Office Action has rejected claims 1-2, 4-5, 7-8 and 11-12 under 35 U.S.C. § 101 allegedly as not having a specific, substantial and credible utility. The Office Action contends that the application describes a nucleotide sequence encoding a polypeptide and an antibody against the polypeptide. But, the Office Action argues, the application does not disclose a biological role for the claimed polypeptide or its significance. The Office Action contends that the asserted utilities as a molecular marker of the integrity of the extracellular matrix or of cartilage integrity, *etc.*, are not considered substantial and specific because the specification fails to disclose any particular function or biological significance for WARP. In brief, the Office Action contends that WARP is said to have a potential function based on its amino acid sequence similarity to other proteins having VA-domains. However, the Office Action argues that further characterization is required to provide a specific, substantial and credible utility. Applicants respectfully traverse this rejection.

Applicants have canceled claims 1-2, 7-8 and 11, rendering the rejection thereto moot. With respect to claims 4, 5 and 12, Applicants assert that the nucleic acid sequence encoding the polypeptide of the instant invention possesses specific, substantial and credible utility. The specification discloses the identification of WARP, a protein that contains a protein domain, the VA (von Willebrand factor A) domain, that is found in extracellular matrix (ECM)

proteins, including collagens, matrilins, and α-integrin proteins, among others. *See*, for example, paragraphs [0007], [0009]. The specification discloses that VA domains play an important role in protein-protein interaction. For instance, the VA-domain in von Willebrand factor interacts with subendothelial heparans, collagens I, III and VI; the VA domain in integrins interacts with several collagens; and in collagen VI the VA domain interacts with heparin and collagen IV. In particular, in collagen VI, a VA domain plays an important role in the assembly of collagen VI tetramers into functional microfibrils. Moreover, in matrilin-1, interchain assembly and microfilament formation is promoted by the interaction of the VA domains in adjacent matrilin molecules. *See*, paragraph [0006]. The specification further discloses that WARP is an oligomeric protein expressed in cartilage. *See*, paragraphs [0150] and [0152] for example. Thus, Applicants assert that the WARP as instantly claimed, which contains these important VA domains, has specific, substantial and credible utility as a marker for extracellular matrix integrity.

In further support, Applicants bring to the attention of the Examiner a recent publication (Allen *et al.*, "WARP is a novel multimeric component of the chondrocyte pericellular matrix that interacts with perlecan," *J. Biol. Chem.*, 2006, 281:7341-7349; "Allen" hereafter; attached herewith at Exhibit 2 and listed on the PTO-1449 form). Allen was coauthored by the inventors of the instant application and describes WARP as a novel multimeric component of the chondrocyte pericellular that contributes to the assembly and/or maintenance of permanent cartilage structures during development and in mature cartilages. As disclosed therein, WARP defines the presumptive articular cartilage prior to joint cavitation and subsequently during development is present in articular cartilage and in fibroocartilage elements. *See*, Allen, p. 7343, col. 2 and FIG. 1). Further, Allen further teaches that WARP interacts with perlecan, a functionally important proteoglycan that is essential for skeletal development and is a component of the cartilage pericellular environment. *See*, Allen, p. 7345-6.

Applicants assert that, given the identification of WARP as a VA-domain containing protein that is involved in a multimeric component of cartilage formation during development, and its interaction with a known, functionally important ECM protein, Applicants have provided a substantial, specific and credible utility as required by 35 U.S.C. § 101. Accordingly, Applicants respectfully request that the Office Action withdraw the rejection.

The Rejections Under 35 U.S.C. § 112 First Paragraph

The Claims Are Enabled And Meet The Written Description Requirement

The Office Action has rejected claims 1-2, 4-5, 7-8 and 11-12 under 35 U.S.C. § 112, 1st paragraph. The Office Action contends that, because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well-established utility, one skilled in the art would not know how to make and use the claimed invention. Applicants submit that, in view of the foregoing reasons articulated with respect to the rejection under 35 U.S.C. § 101, a well-established utility is supported and, as such, one ordinarily skilled in the art would know how to make and use the claimed invention.

Further, the Office Action asserts, that there is insufficient guidance and direction as to how to make the claimed polypeptide or a derivative or homolog thereof, encoded by any nucleic acid sequence having at least about 65% similarity to SEQ ID NO:1 or 5 or capable of hybridizing to SEQ ID NO:1 or 5 under low stringency conditions. Without detailed description, the Office Action contends, a person of ordinary skill in the art would not be able to determine, without undue experimentation, which nucleic sequences encompassed by the instant claims would share the ability as a molecular marker of degenerative disease, other than SEQ ID NO:5 encoding SEQ ID NO:6. The Office Action further contends that the open "comprising" language opens up the claimed molecule to unspecified amino acids/nucleic acids on either or both termini of the molecule.

For the same reasons articulated above with respect to the written description requirement, the Office Action contends that the claims are not enabled. Applicants respectfully traverse these rejections and respond to them both herein.

Applicants have canceled claims 1-2, 7-8 and 11, rendering the rejections thereto moot. Applicants have further amended claim 4 to delete the feature of a nucleic acid having at least about 65% similarity to SEQ ID NO:5 or capable of hybridizing to SEQ ID NO:5 under low stringency conditions. Applicants have further amended claim 4 to recite a nucleic acid sequence that hybridizes to SEQ ID NO:5 or the complement thereof under high stringency conditions. Applicants assert that it is well within the skill of one in the art to identify a nucleic

acid or polypeptide sequence having the similarity as claimed in the instant claims. For instance, the specification teaches that the EST database at the National Center for Biotechnology Information (NCBI) was searched using the N8 VA-domain protein sequence as a query to identify EST sequences that contain the VA-domain. *See*, paragraph [0010]. The specification teaches that a series of overlapping EST clones with homology to N8 represented a novel VA protein, therein entitled WARP. *See*, paragraphs [0131] and [0153].

With respect to the contention that Applicants have not enabled or provided written description for "a homolog or derivative thereof," Applicants respectfully traverse. Applicants disclose a mouse WARP as a homolog of human WARP. As disclosed in paragraph [0045], "[a] homolog of murine origin comprises a VA-related domain having the amino acid sequence set forth in SEQ ID NO:8." Further, a "homolog" is defined as "an analogous polypeptide having at least about 65% similar amino acid sequence from another animal species or from a different locus within the same species." *See*, paragraph [0050]. Moreover, as disclosed in paragraph [0142], "[t]he human homolog of WARP was identified by searching the genome data with the mouse WARP protein sequence. A match with a predicted protein sequence (hypothetical protein FJL22215) with very high homology to the mouse WARP was found .... These sequences are clearly homologs of each other because they share 79% amino acid identity (*see* Figure 1C). In addition, if conserved changes are considered in the analysis, they share 95% identity."

In addition, Applicants submit that "a derivative" is supported by the specification as filed. A "derivative" is defined in paragraph [0049] to include "a mutant, fragment, part, portion or hybrid molecule. A derivative generally carries a single or multiple amino acid substitutions, addition and/or deletion." Furthermore, Applicants provide ample teaching of modifications to amino acids of the instant invention which can provide the amino acid substitution of a derivative. *See*, for example paragraphs [0053] to [0058] which disclose amino acid side chain modifications and which were well known to one of ordinary skill in the art at the time of filing. Moreover, paragraph [0059] and Table 1 teaches incorporating unnatural amino acids and derivatives during polypeptide synthesis.

Applicants submit that the specification provides ample written description to support the claims as amended, and that further, one of ordinary skill in the art would, at the time

of filing, know how to make and use the instant invention. Accordingly, Applicants respectfully request that the Examiner withdraw the enablement and written description rejections under 35 U.S.C. § 112, first paragraph.

The Rejections Under 35 U.S.C. § 102

The Claims Are Not Anticipated By WO2001/018022

The Office Action contends that claims 1-2, 4, 7-8 and 11 are rejected under 35 U.S.C. § 102(b) as anticipated by International Patent Publication No. WO2001/018022 ("the '022 publication") filed August 31, 2000. The Office Action contends that the '022 publication teaches (i) a polypeptide encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO:1, the nucleic acid sequence would hybridize to SEQ ID NO:1 or 5 under low stringency conditions; (ii) a polypeptide encoded by a nucleic acid sequence having at least 99% similarity to SEQ ID NO:5, said nucleic acid sequence would hybridize to the complement of SEQ ID NO:5 at low stringency conditions; (iii) a 215-amino acid polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein the 215-amino acid polypeptide has 99.5% similarity to SEQ ID NO:6. As such, the Office Action contends that the '022 publication anticipates the claimed invention.

Applicants have canceled claims 1-2, 7-8 and 11, rendering the rejection thereto moot. Applicants submit that the amended claims are not anticipated by the '022 publication. The '022 publication discloses a amino acid sequence (SEQ ID NO:85), that encodes a 215-amino acid polypeptide. The amino acid of SEQ ID NO: 85 is encoded by nucleic acid sequence of SEQ ID NO: 13. SEQ ID NO: 13 refers to a nucleic acid sequence 734 nucleotides in length. In contrast, SEQ ID NO:6 of the instant specification refers to a 418-amino acid polypeptide. The '022 publication does not disclose a 418-amino acid polypeptide having the identical sequence as disclosed in the instant application under SEQ ID NO:6. Moreover, SEQ ID NO:5 of the instant invention refers to a 1254-nucleotide nucleic acid sequence. The '022 publication does not disclose a nucleic acid sequence having the identical sequence as disclosed in the instant specification under SEQ ID NO:5. As such, the '022 cannot anticipate the claims as presently amended. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under U.S.C. § 102(b).

The Claims Are Not Anticipated By US20060003323

The Office Action contends that claims 1-2, 4, 7-8 and 11 are rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent Publication No. US2006/0003323 ("the '323 publication"). The Office Action contends that the '323 publication teaches (i) a polypeptide encoded by a nucleic acid sequence that is 100% identical to SEQ ID NO:1, the nucleic acid sequence would hybridize to SEQ ID NO:1 or 5 under low stringency conditions; (ii) a polypeptide encoded by a nucleic acid sequence having at least 93% similarity to SEQ ID NO:5, the nucleic acid sequence would hybridize to the complement of SEQ ID NO:5 at low stringency conditions; (iii) a 445-amino acid polypeptide comprising the amino acid sequence of SEQ ID NO:2, and that the 445-amino acid polypeptide has 93% similarity to SEQ ID NO:6. As such, the Examiner contends that the '323 publication anticipates the claimed invention.

Applicants have canceled claims 1-2, 7-8 and 11, rendering the rejection thereto moot. Applicants submit that the amended claims are not anticipated by the '323 publication. The '323 publication discloses a amino acid sequence (SEQ ID NO:2), which encodes a 445-amino acid polypeptide. The amino acid of SEQ ID NO: 2 is encoded by nucleic acid sequence of SEQ ID NO:1. SEQ ID NO:1 refers to a nucleic acid sequence 4494 nucleotides in length. In contrast, SEQ ID NO:6 of the instant application refers to a 418-amino acid polypeptide. The '323 publication does not disclose a 418-amino acid polypeptide having the identical sequence as disclosed in the instant application under SEQ ID NO:6, or a nucleic acid sequence having the identical sequence as disclosed in the instant application under SEQ ID NO:5. As shown in the alignment submitted herewith at Exhibit 3, an alignment of the nucleic acid sequence of SEQ ID NO:5 of the instant invention with the nucleic acid sequence of SEQ ID NO:1 of the '323 publication shows that the sequences are only 86% similar overall. As such, the '323 publication cannot anticipate the claims as presently amended. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under U.S.C. § 102(e).

Formal Request for an Interview

Applicants respectfully request entry of the above amendments, consideration of the remarks made herein, and allowance of the pending claims. Applicants submit that the present application is in condition for allowance at least for the reasons set forth herein. If the present application is not considered to be in condition for allowance by the Examiner, Applicants request an interview with the Examiner to discuss the present application and the prior art of record. Applicant's Attorney Walter M. Egbert may be reached at telephone number (212) 408-2500 to schedule a mutually convenient date and time and to provide assistance or additional information as required.

Conclusion

Applicants believe that no additional fee is due in connection with filing of this Response. However, if any fee is required, or if any overpayment has been made, Applicants authorize, in the Transmittal Form and Fee Transmittal (submitted herewith in duplicate), the Director to charge any fees, or credit or any overpayments made, to Deposit Account 02-4377.

Respectfully submitted,

Oct. 2, 2006
Date

Kimberley A. Gavin, Reg. No. 51,723
Agent for Applicants

Lisa B. Kole, Reg. No. 35,225
Attorney for Applicants

BAKER BOTTS L.L.P
Customer No. 21003
30 Rockefeller Plaza
New York, NY 10112
(212)-408-2500

APPENDIX